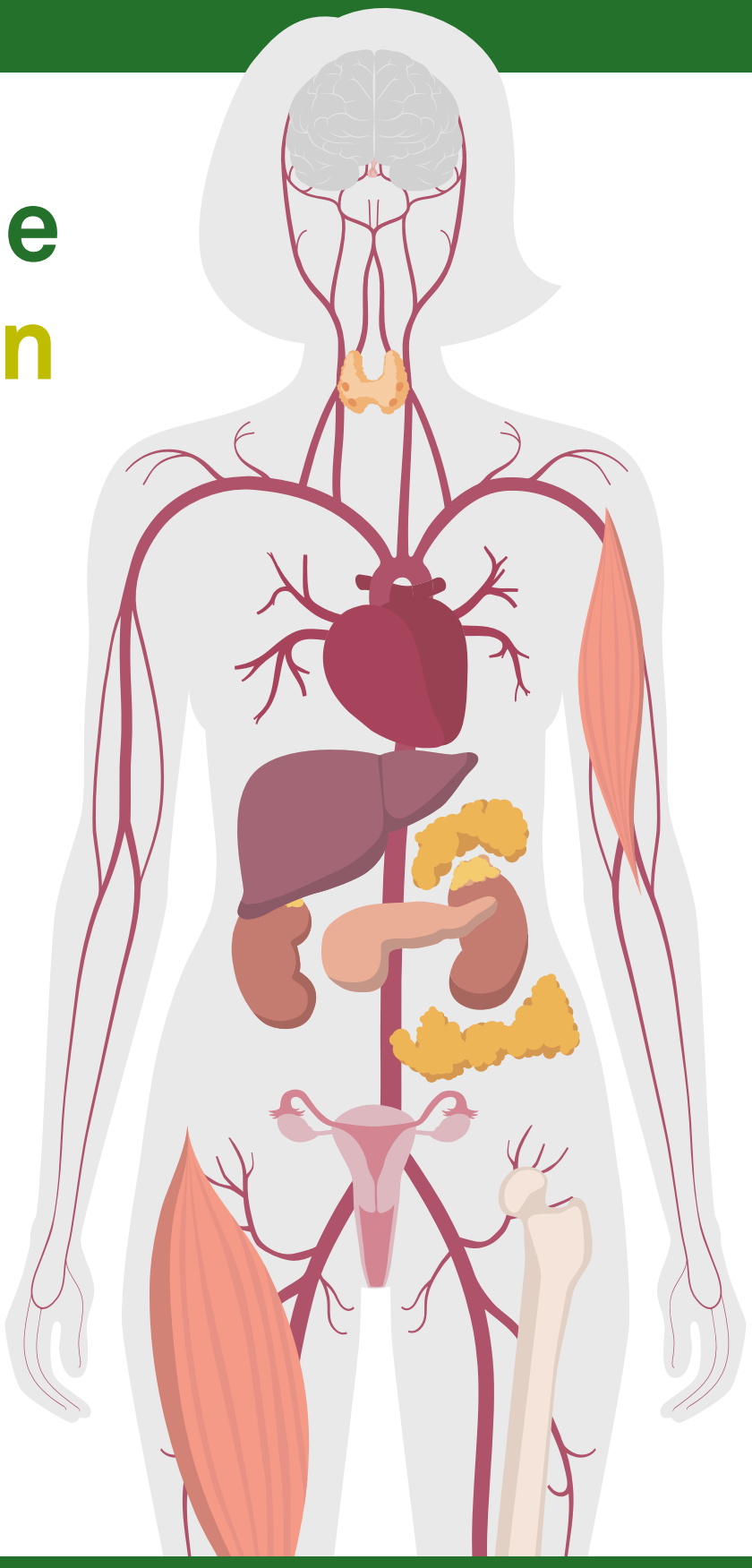
Quest Diagnostics®

Quest® Cardiometabolic Center of Excellence™ at ClevelandHeartLab®

Defining the intersection of chronic conditions

The evidence demonstrating the interrelationships between chronic cardiometabolic diseases continues to expand, supporting a personalized approach to reducing risk.

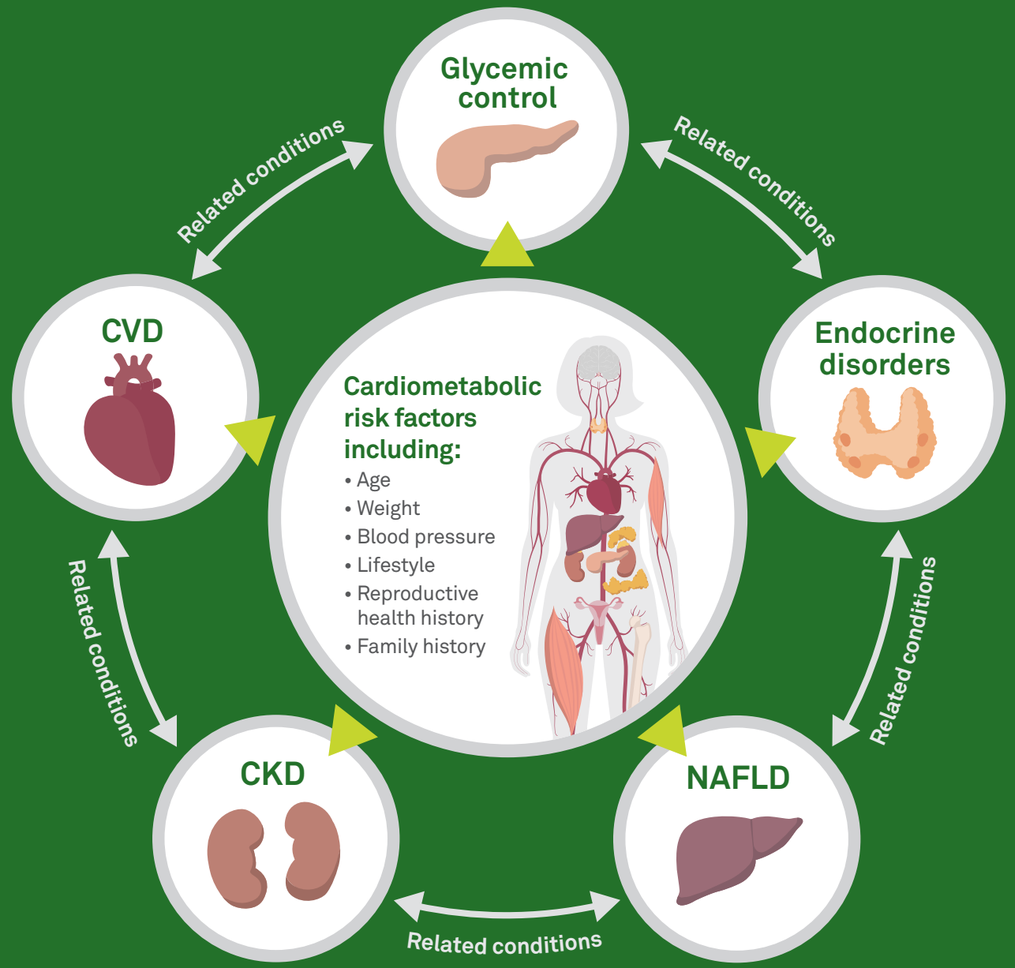
- Type 2 diabetes
- Nonalcoholic fatty liver disease
- Chronic kidney disease
- Cardiovascular disease
- Common endocrine disorders



Introduction

The epidemic of chronic disease

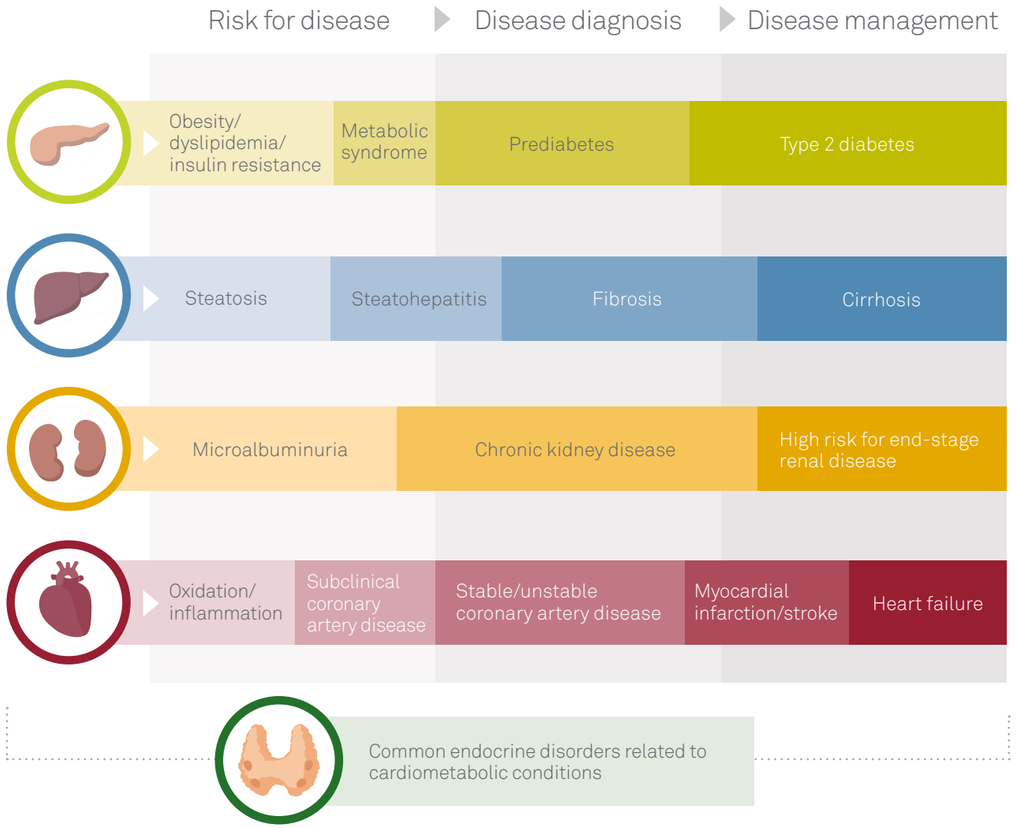
It is estimated that as many as 45% of Americans have a chronic disease; more than half of older adults have 3 or more chronic conditions. There are shared cardiometabolic risk factors contributing to related conditions, such as cardiovascular disease, poor glycemic control, chronic kidney disease, fatty liver disease, and common endocrine disorders.



Improve clinical outcomes through early **identification, accurate diagnosis, and intervention**

The related chronic cardiometabolic conditions are characterized by initial stages that may remain clinically silent for years. These chronic conditions can be influenced and sometimes exacerbated by common endocrine conditions. A comprehensive test menu spanning the continuum from early identification of cardiometabolic risk and accurate endocrine disorder diagnosis allows providers to personalize the risk assessment and implement evidence-based strategies that can prevent or delay disease progression and related complications.

Related conditions across the cardiometabolic risk continuum



Type 2 Diabetes

Scope of the problem[1]

96 million
are at risk for type 2 diabetes (T2DM)

37 million
are estimated **to have T2DM**

8.5 million
cases of T2DM are **undiagnosed**

Why the epidemic of T2DM?

- More than one third of adults are obese. An additional third are overweight[1]
- Insulin resistance, the first step in the progression of disease, may be overlooked clinically, resulting in the identification of metabolic dysfunction at a later stage (prediabetes or T2DM), when hyperglycemia is detected[2]
- The conditions related to metabolic dysfunction and T2DM often go undiagnosed and untreated. These include CVD, CKD, NAFLD, and common endocrine disorders

Pathophysiology

Healthy (insulin sensitive)

Insulin is produced by pancreatic beta cells to signal the uptake of glucose into target cells, such as those in fat, muscle, and the liver.

Insulin resistance

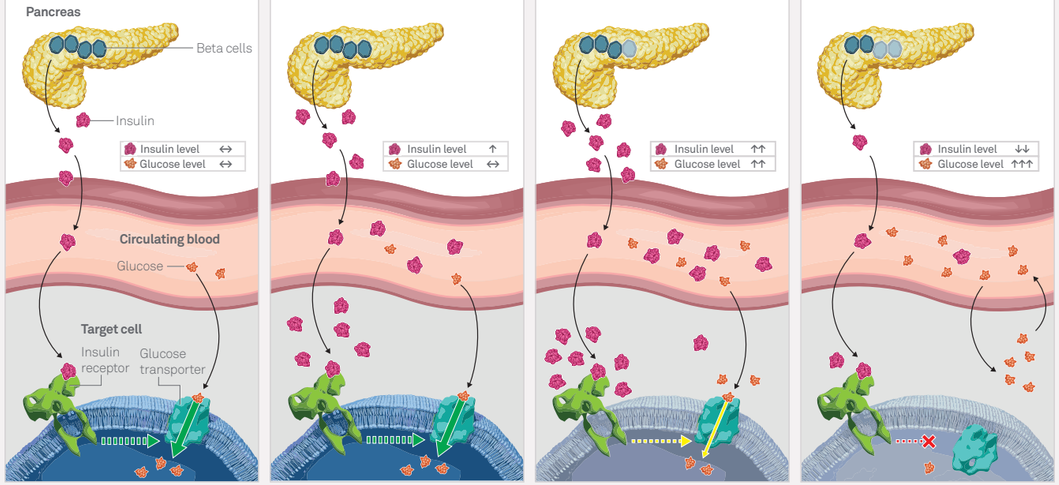
In insulin resistance, target cells "resist" the action of insulin to signal glucose uptake. Higher amounts of insulin are required to maintain normoglycemia.

Prediabetes

As insulin resistance worsens, beta cells produce increasing amounts of insulin, causing them to fatigue. Insulin-mediated uptake of glucose is diminished, leading to hyperglycemia.

Type 2 diabetes

The overworked beta cells die, resulting in less insulin production, which further diminishes insulin-mediated glucose uptake and leads to worsening hyperglycemia.



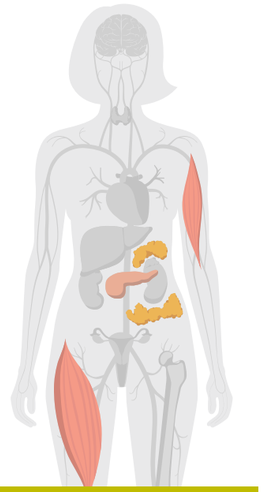
Indicators of risk for T2DM

Risk factors for T2DM[3-5]

- Age >35 years old
- Overweight or obese
- Hypertension
- Unhealthy lifestyle habits
- History of adverse pregnancy outcomes
- Erectile dysfunction
- Family history
- Ethnic heritage
- Acanthosis nigricans

Conditions associated with increased risk of T2DM[3,6-10]

- Insulin resistance
- Polycystic ovary syndrome (PCOS)
- Testosterone deficiency
- Thyroid dysfunction
- Primary aldosteronism
- CVD
- CKD
- NAFLD



	Test codes			The following tests may help:	
	Quest Diagnostics accounts	**Cleveland HeartLab accounts**	**Biomarker**	**Identify metabolic risk**	**Diagnose and manage prediabetes and T2DM**
Glycemic-based	36509	36509	Insulin Resistance Panel with Score	x	
	93103	NA	Insulin, Intact, LC/MS/MS	x	x
	91731	C146	Insulin Immunoassay (IA)	x	x
	23475	C505	Glucose Tolerance Test, 3 Specimens (75g)	x	x
	372	C136	C-Peptide Immunoassay (IA)		x
	91947	C101	Glucose		x
	91732	C145	Hemoglobin A1c		x
	8340	8340	Fructosamine		x
Lipid-based	91716	C906	Lipid Panel	x	
	91604	1346	Lipoprotein Fractionation, Ion Mobility	x	
	37847	37847	Lipoprotein Fractionation, NMR	x	
	91726	C123	Apolipoprotein B (ApoB)	x	
	92769	C335	Oxidized LDL (OxLDL)	x	
Other	39447	39447	Metabolic Risk Panel	x	x
	15060	C314	Adiponectin	x	
	90367	90367	Leptin	x	
	91735	C339	Vitamin D, 25-Hydroxy	x	

Panel components may be ordered separately:

Insulin Resistance Panel with Score: The panel component Insulin, Intact, LC/MS/MS (93103) can be ordered separately. The C-peptide LC/MS/MS panel component cannot be ordered separately

Lipid Panel: Cholesterol, Total (91717, C117); Triglycerides (91718, C119); HDL Cholesterol (91719, C118)

Metabolic Risk Panel: Cholesterol, Total (91717, C117); Triglycerides (91718, C119); HDL Cholesterol (91719, C118); Lipid Panel (91716, C906); Hemoglobin A1c (91732, C145); Apolipoprotein B (91726, C123); Insulin, Intact, LC/MS/MS (93103); Insulin Resistance Panel with Score (36509, 1388)

Nonalcoholic Fatty Liver Disease

Scope of the problem[10,11]

100 million
are estimated to have NAFLD

6.6 million
will eventually have liver fibrosis

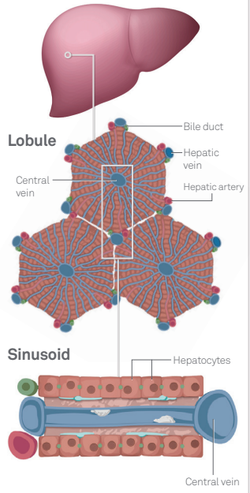
<5%
of NAFLD cases have been **diagnosed**

Factors contributing to prevalence and outcomes of NAFLD or MASLD

- Rising rates of metabolic dysfunction, obesity, and type 2 diabetes mellitus (T2DM) contribute to increased prevalence of nonalcoholic fatty liver disease (NAFLD), also known as metabolic dysfunction-associated steatotic liver disease (MASLD)
  - Hyperinsulinemia has been shown to contribute to the development of NAFLD[12]
- Early NAFLD is clinically silent
- Advanced stages (fibrosis/cirrhosis) can result in
  - liver failure, ultimately requiring transplant
  - liver cancer
  - risk for coronary artery disease

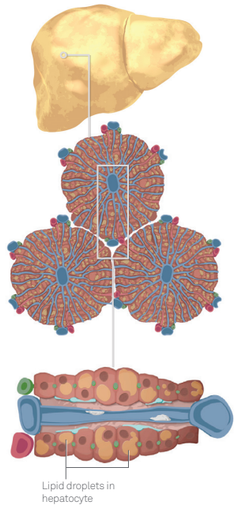
Pathophysiology

Healthy liver



Each liver segment is divided into hexagonal arrangements of hepatocytes called *lobules*. The hepatocytes radiate from a central vein. The spaces between the plates of hepatocytes are called *sinusoids*.

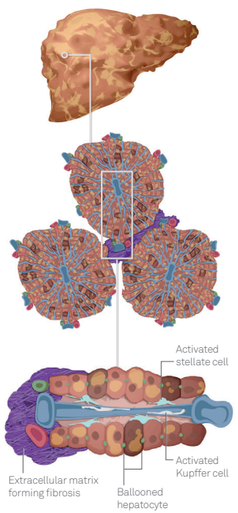
Steatosis (fatty liver)



Certain metabolic factors, including type 2 diabetes, obesity, insulin resistance, and/or a surplus of caloric and dietary fat intake, result in excess release of fatty acids into the bloodstream. These fatty acids, in the form of triglycerides, accumulate in hepatocytes, via

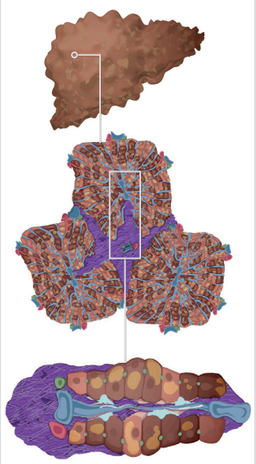
- increased hepatic lipogenesis
- decreased expulsion of hepatic lipid stores
- diminished oxidation of free fatty acids in the liver

Early nonalcoholic steatohepatitis (NASH)



The fat-storing capacity of hepatocytes becomes overwhelmed, leading to lipotoxicity and causing cellular damage and the release of liver enzymes (ALT, AST). Lipotoxic metabolites, elevated levels of cholesterol and uric acid, comorbid sleep apnea, and dysregulation of the gut microbiome all contribute to oxidative stress. The resulting inflammatory responses include the activation of stellate cells, which begin to lay down extracellular matrix (ECM).

Late NASH with fibrosis



Excessive ECM deposition can lead to advanced liver fibrosis, cirrhosis, and ultimately liver failure (requiring transplantation) and hepatocellular carcinoma.

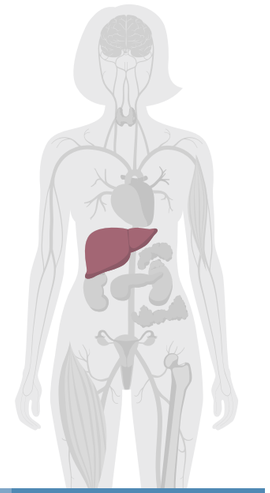
Indicators of risk for NAFLD

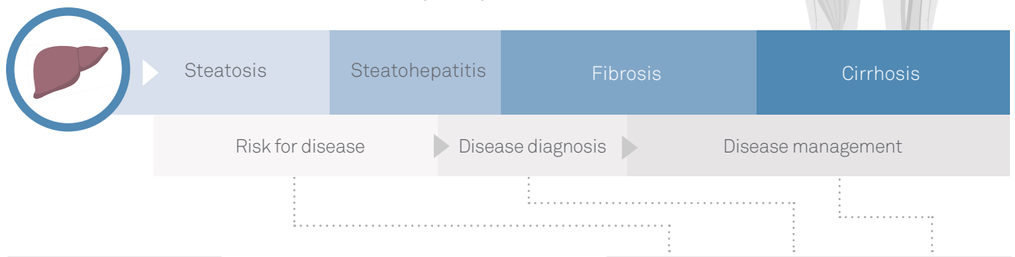
Risk factors for NAFLD[10,11]

- Overweight or obese
- Central adiposity
- Hypertension
- Family history of cirrhosis
- History of elevated AST or ALT
- History of steatosis identified by imaging or biopsy

Conditions associated with increased risk of NAFLD[10-14]

- Insulin resistance
- Metabolic syndrome
- Diabetes
- CVD
- CKD
- Dyslipidemia
- Sleep apnea
- PCOS
- Testosterone deficiency
- Thyroid dysfunction





Test codes*			The following tests may help identify:		
Quest Diagnostics accounts	**Cleveland HeartLab accounts**	**Biomarker**	**Risk of steatosis or steatohepatitis (fibrosis F0-F2)**	**Risk of advanced fibrosis (F3-F4)**	**Risk of progression to cirrhosis or liver-related events**
93103	NA	Insulin, Intact, LC/MS/MS	x		
823	C112	Alanine Aminotransferase (ALT)	x	x	x
822	C113	Aspartate Amino Transferase (AST)	x	x	x
30555	30555	Liver Fibrosis, FIB-4 Index Panel		x	
12734	NA	FIB-4 Index Panel with Reflex to Enhanced Liver Fibrosis (ELF) Score*		x	x
10372	10372	Comprehensive Metabolic Panel with FIB-4 Index		x	
12736	NA	Comprehensive Metabolic Panel with FIB-4 Index with Reflex to ELF Score*		x	x
30710	30710	Liver Fibrosis, Hepatic Function Panel with FIB-4 Index		x	
12735	NA	Hepatic Function Panel with FIB-4 Index with Reflex to ELF Score*		x	x
10350	10350	Enhaced Liver Fibrosis (ELF) Score			x

*For each panel, if FIB-4 Index is ≥1.30, then Enhanced Liver Fibrosis (ELF) Score (10350) will be performed at an additional charge.

Panel components may be ordered separately:

FIB-4 Index Panel: AST (822, C113); ALT (823, C112); and Platelet Count (723, 1380)

Comprehensive Metabolic Panel with FIB-4 Index: Urea Nitrogen (BUN) (294, C107); Creatinine (375, C108) with GFR Estimated; BUN/Creatinine Ratio (calculated) (296, 2968); Glucose (483, C101); Potassium, Serum (733, C104); Sodium (836, C103); Calcium (303, C102); Carbon Dioxide (310, C105); Chloride (330, C106); Total Protein (754, C110); Albumin (223, C109); Globulin (calculated); Albumin/Globulin Ratio (calculated); Total Bilirubin (287, C114); Alkaline Phosphatase (234, C111); AST (822, C113); ALT (823, C112); Platelet Count (723, 1380)

Liver Fibrosis Hepatic Function Panel with FIB-4 Index: Total Protein (754, C110), Albumin (223, C109), Globulin (calculated), Albumin/Globulin Ratio (calculated), Total Bilirubin (287, C114), Direct Bilirubin (285, C115), Indirect Bilirubin (calculated), Alkaline Phosphatase (234), AST (822, C113), ALT (823, C112), Platelet Count (723, 1380)

Chronic Kidney Disease

Scope of the problem[15,16]

80 million
are at risk for chronic kidney disease (CKD)

37 million
are afflicted with CKD

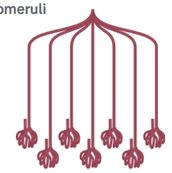
Nearly 40%
of patients who have stage 4 CKD remain **unaware of their diagnosis**

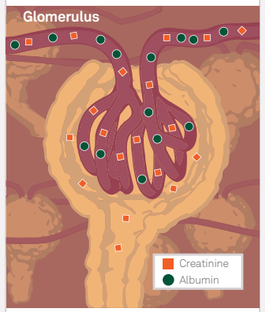
Factors underlying the increase in the prevalence of CKD

- The rising prevalence of metabolic dysfunction and number of individuals with hypertension are the two leading risk factors for CKD[15]
- Despite efforts to raise awareness and reduce CKD progression, the prevalence of CKD stages 1-4 increased from 11.8% to 14.2% over the past 25 years[15]
- Screening is crucial, as 9 in 10 adults with CKD don't know they have it,[15] causing late-stage diagnosis and 1 in 4 patients to "crash" into dialysis[17]

Pathophysiology

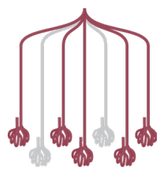
Healthy kidney

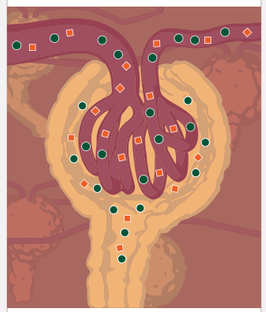




The glomerulus filters blood particles according to their size and charge. In the healthy kidney, only creatinine (not albumin) is filtered through the kidney and excreted in the urine.

Kidney with albuminuria

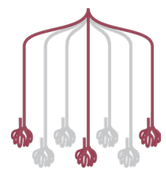


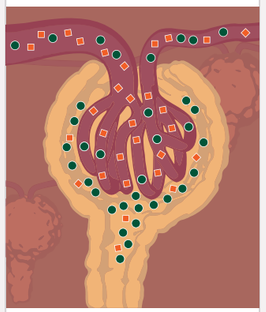


As the number of functioning glomeruli decreases, the remaining healthy glomeruli compensate by increasing the glomerular filtration rate (compensatory hyperfiltration).

Damage to the glomeruli results in albumin leaking into the urine, detected as an increase in the urine albumin to creatinine ratio (uACR).

Kidney with eGFR decrease



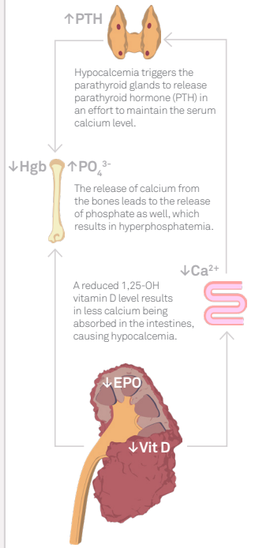


The number of functioning glomeruli continues to decrease; hyperfiltration can no longer compensate, and the serum creatinine level increases.

Over time, individual glomeruli cease to function, resulting in a decrease in the overall filtering capacity of the kidney. This results in a reduced glomerular filtration rate leading to higher average serum creatinine levels. Moderate albuminuria progresses to severe albuminuria.

Kidney decline with complications

As CKD progresses, the impact of decreased kidney function is manifested in various body systems.



Decreased synthesis of erythropoietin (EPO) results in anemia.

As kidney function declines, the kidney's ability to convert 25-OH vitamin D to its active form, 1,25-OH vitamin D, becomes impaired.

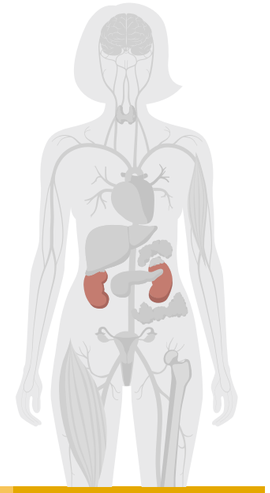
Indicators of risk for CKD

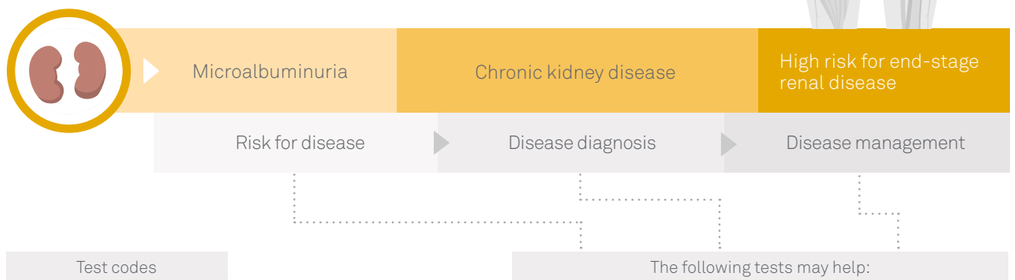
Risk factors for CKD[15,18]

- Age (≥60 y)
- Overweight or obese
- Hypertension
- Family history of kidney disease
- Ethnic heritage
- Smoking
- Frequent use of medications that can damage kidneys

Conditions associated with increased risk of CKD[9,15,19-22]

- Diabetes
- Kidney or urinary tract abnormalities
- Chronic inflammatory/autoimmune diseases
- Primary aldosteronism
- Testosterone deficiency
- Thyroid dysfunction
- CVD
- NAFLD





Test codes			The following tests may help:		
Quest Diagnostics accounts	**Cleveland HeartLab accounts**	**Biomarker**	**Identify early risk for kidney damage**	**Confirm kidney damage**	**Manage kidney disease and measure the extent of kidney decline**
375	C108	Creatinine with eGFR	x	x	x
6517	NA	Urine Albumin/Creatinine Ratio (uACR)	x	x	x
39165	39615	Kidney Profile (eGFR + uACR)	x	x	x
94588	94588	Cystatin C with eGFR		x	x
510	C211	Hemoglobin			x
310	C105	Carbon Dioxide			x
733	C104	Potassium, Serum			x
17306	C339	Vitamin D, 25-Hydroxy			x
16558	C1572	Vitamin D, 1,25-Dihydroxy			x
8837	C309 & C102	PTH, Intact and Calcium			x
718	C116	Phosphate (as Phosphorus)			x

Panel components may be ordered separately:

Kidney Profile: eGFR (375), Albumin, Random Urine with Creatinine (6517)

Cardiovascular Disease

Scope of the problem[23-25]

202 million
are at risk for cardiovascular disease (CVD)

153 million
are estimated **to have CVD**

26 million
cases of CVD have been **diagnosed**

Why the magnitude of the CVD epidemic?

- Increased prevalence of prediabetes, type 2 diabetes (T2DM), and overweight/obesity contributes to dyslipidemia, hypertension, and atherosclerotic disease progression
- Although the manifestation of CVD is often sudden, the progression from the initial atherosclerotic lesion (fatty streak) to symptomatic disease spans decades
- Standard CVD risk assessment tools such as a lipid panel often do not identify the long, clinically silent period of atherosclerotic progression
- Cardiovascular disease is an often fatal end-stage consequence of the associated chronic cardiometabolic conditions T2DM, chronic kidney disease (CKD), and nonalcoholic fatty liver disease (NAFLD)

Pathophysiology

1 Healthy blood vessel
- The blood vessel wall is separated from the lumen by a thin, smooth endothelium

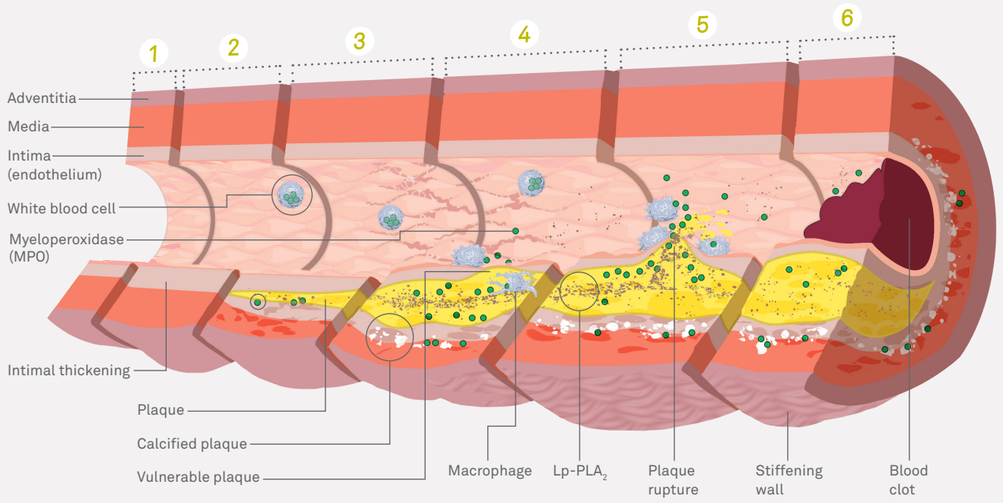
2 Oxidation
- Poor diet and lifestyle can contribute to oxidative stress, making the blood vessel more susceptible to damage and plaque formation, and is associated with metabolic syndrome risk

3 Plaque accumulation and endothelial damage
- LDL-cholesterol particles, damaged from oxidation, collect within the vessel wall, forming plaque (fatty deposits)
- Injury to the vessel lining leads to endothelial dysfunction and increased plaque burden

4 Disease activity and vulnerable plaque
- The immune response to lipid and inflammatory cell accumulation contributes to an active necrotic lipid core and a thinning fibrous cap, rendering the plaque vulnerable to rupture

5 Plaque rupture
- Eruption of plaque into the lumen triggers an immune response to heal the site of rupture

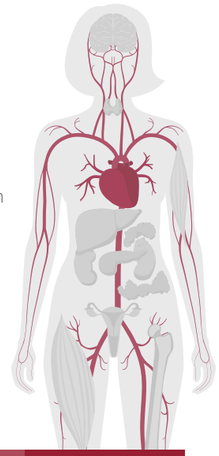
6 Myocardial Infarction/stroke
- A thrombus (blood clot) can form at the site of plaque rupture, blocking blood flow and resulting in a heart attack or stroke

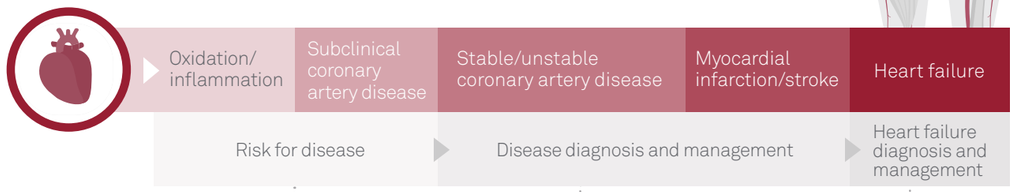


Indicators of risk for CVD

Risk factors for CVD[26-28]
- Age (>45 y, men; >55 y, women)
- Overweight or obese
- Hypertension
- Unhealthy lifestyle habits
- History of adverse pregnancy outcomes
- Erectile dysfunction
- Family history
- Ethnic heritage
- Smoking
- Sleep duration, poor sleep quality

Conditions associated with increased risk of CVD[9,26-33]
- Dyslipidemia
- Insulin resistance
- Chronic inflammatory conditions/ autoimmune disease
- Periodontal disease
- Depression
- Sleep apnea
- PCOS
- Testosterone deficiency
- Thyroid dysfunction
- Primary aldosteronism
- Diabetes
- CKD
- NAFLD
- Menopause





	Test codes			The following tests may help:		
	Quest Diagnostics accounts	**Cleveland HeartLab accounts**	**Biomarker**	**Identify risk of CVD**	**Diagnose or manage CVD**	**Identify, diagnose, or manage heart failure**
Lipids	91716	C906	Lipid Panel	x	x	x
	92061	C909	Lipid Panel with Reflex to Direct LDL	x	x	x
	91604	1346	Lipoprotein Fractionation, Ion Mobility	x	x	
	37847	37847	Lipoprotein Fractionation, NMR	x	x	
	91726	C123	Apolipoprotein B (Apo B)	x	x	
	91727	C511	ApoB/ApoA1 Ratio	x	x	
	36406	1341	sdLDL	x	x	
	91729	91729	Lipoprotein (a)	x	x	
	NA	37812	HDL Function Panel with HDLfx pCAD Score	x	x	
Inflammation	92771	C261	F_2-Isoprostane/Creatinine Ratio	x		
	92769	C335	Oxidized LDL (OxLDL)	x		
	NA	C919	Microalbumin/Creatinine Ratio	x		
	91737	C121	hs-CRP	x	x	
	94153	C301	ADMA/SDMA	x	x	
	94218	94218	Lp-PLA_2 Activity	x	x	
	92814	C133	Myeloperoxidase (MPO)	x	x	
Other	92701	C302	OmegaCheck®	x		
	19826	C295	Coenzyme Q10	x		
	91733	C308	Homocysteine	x		
	91743	C334	Fibrinogen Antigen, Nephelometry	x		
	94154	C524	TMAO (Trimethylamine N-oxide)	x		
	16174	C922	AspirinWorks® 11-Dehydrothromboxane B2 (11-dhTXB2) with Creatinine	x	x	
	38685	38685	Troponin T, High Sensitivity (hs-TnT)		x	
	91739	C125	NT-ProBNP	x	x	x
	92768	C315	Galectin-3			x
	94220	NA	Advanced Lipid Panel with Inflammation	x	x	x

Panel components may be ordered separately:

Lipid Panel: Cholesterol, Total (91717, C117); Triglycerides (91718, C119); HDL Cholesterol (91719, C118)

Lipid Panel with Reflex to Direct LDL: Cholesterol, Total (91717, C117); Triglycerides (91718, C119); HDL Cholesterol (91719, C118). If triglyceride result is >400 mg/dL, Direct LDL Cholesterol will be performed at an additional charge

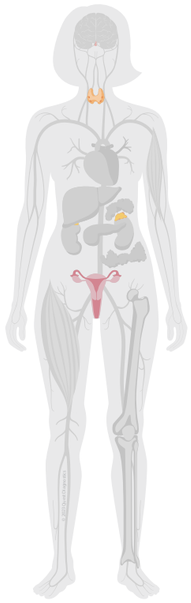
ApoB/ApoA1 Ratio: Apolipoprotein B (91727, C123), Apolipoprotein A1 (91724, C122)

HDL Function Panel with HDLfx pCAD score: AALP ApoA-I (37838); AALP ApoC-I (37864); AALP ApoC-II (37865); AALP ApoC-III (37866); AALP ApoC-IV (37867)

Advanced Lipid Panel with Inflammation: Cholesterol, Total (91717); Triglycerides (91718); HDL Cholesterol (91719); Lipoprotein Fractionation, Ion Mobility (91604); Apolipoprotein B (91726); Lipoprotein (a) (91729); hs-CRP (91737); Lp-PLA_2 Activity (94218). If triglyceride result is >400 mg/dL, Direct LDL Cholesterol will be performed at an additional charge

Common Endocrine Disorders

Endocrine disorders are a group of medical conditions that occur as a result of abnormal hormone levels in the body. The change in hormones that occurs in common endocrine disorders can lead to a wide range of physiological and metabolic abnormalities that are related to cardiometabolic conditions.



Thyroid disorders

Hyperthyroidism/ hypothyroidism

Cardiometabolic connection:

- An excess or deficiency of thyroid hormones may incite or worsen CVD[34]
- Thyroid disorders are associated with dyslipidemia, heart failure, hypertension, hyperglycemia, and hyperinsulinemia[34,35]
- The risk of NAFLD increases 42% among patients who have hypothyroidism[36]
- Hypothyroidism is associated with a lower eGFR level and reduced kidney function[37]

Clinical presentation: fatigue, weight gain/loss, anxiety, or depression

Key hormones: TSH, T4, T3

Adrenal disorders

Primary aldosteronism

Cardiometabolic connection:

Compared with individuals who have essential hypertension, those who have primary aldosteronism are at higher risk of

- coronary artery disease, heart failure, stroke, and atrial fibrillation[8]
- microalbuminuria, overt proteinuria, CKD, and greater annual eGFR decline despite treatment with mineralocorticoid antagonists[19,38]
- diabetes and metabolic syndrome[8]

Clinical presentation: hair loss, hypertension

Key hormones: aldosterone, plasma renin activity, aldosterone/ plasma renin activity ratio

Endocrine reproductive disorders

Polycystic ovary syndrome

Cardiometabolic connection:

- Compared with women who do not have PCOS, those who have the disorder have a higher risk of having hypertension, metabolic syndrome, and cardiovascular disease earlier in life[39,40]
- More than half of women who have PCOS develop T2DM by age 40[41]
- Women who have PCOS have a 2 to 4 times greater risk of NAFLD[11]

Clinical presentation: hirsutism, oligomenorrhea, obesity, insulin resistance, infertility

Key hormones: testosterone, prolactin, 17-OH progesterone, TSH with reflex to free T4

Hypogonadism

Cardiometabolic connection:

Men who have a low testosterone level have a 4 times greater risk of diabetes[42] and have an increased likelihood of having NAFLD.[13]

Testosterone deficiency is also associated with hypertension and atherosclerotic CVD.[43]

Among men who have CKD,[44]

- 50% have a decreased testosterone level
- reduced testosterone is associated with increased mortality

Clinical presentation: erectile dysfunction, decreased libido, decreased muscle mass, fatigue

Key hormones: testosterone, prolactin, FSH, LH

Infertility

Cardiometabolic connection:

Compared with fertile women, those who are infertile were about 2 times more likely to have diabetes[45] or metabolic syndrome[46] or suffer a cardiovascular event.[45]

Compared with fertile men, those who are infertile have a[47]

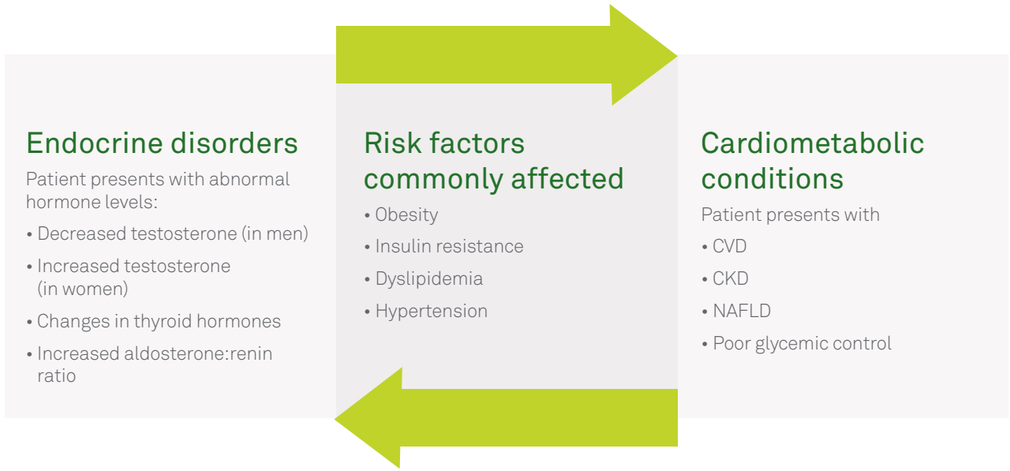
- 50% higher risk of ischemic heart disease
- 30% higher risk of CKD and diabetes

Clinical presentation: inability to conceive after 1 year if younger than 35 years or after 6 months if older than 35

Key hormones: prolactin, FSH, LH, estradiol (women), testosterone (men)

Understanding the relationship of endocrine disorders with cardiometabolic conditions

The endocrine system consists of a network of hormones that regulate body functions such as growth, reproduction, metabolism, and the stress response. The disruption or imbalance of hormone levels can result in physiological and metabolic dysfunction, affecting cardiometabolic health. Conversely, patients who present with cardiometabolic conditions may have risk factors that are influenced by abnormal hormone levels.



Test codes

	Quest Diagnostics accounts	Cleveland HeartLab accounts	Biomarker
Thyroid	899	C157	TSH
	866	C142	T4 Free (FT4)
	36127	C513	TSH with reflex to Free T4
	58984	NA	TSH and Free T4
	859	C144	T3, Total
Adrenal	17180	1263	17-Hydroxyprogesterone
	4212	1434	Cortisol, A.M.
	16845	NA	Aldosterone/Plasma Renin Activity Ratio, LC/MS/MS
	17181	17181	Aldosterone, LC/MS/MS
	16846	NA	Plasma Renin Activity, LC/MS/MS
Reproductive hormones	15983	15983	Testosterone, Total, MS
	36170	1300	Testosterone, Free (Dialysis) and Total, MS
	14966	1043	Testosterone, Free, Bioavailable and Total, MS
	30289	NA	Estradiol, Ultrasensitive, LC/MS
	17183	NA	Progesterone, LC/MS
	470	C317	FSH (Follicle Stimulating Hormone)
	615	C149	LH
	7137	NA	FSH and LH
	746	C327	Prolactin

Panel components may be ordered separately:

Testosterone, Free, Bioavailable and Total, MS: Includes total (15983) and free (18944) and bioavailable testosterone, sex hormone binding globulin (30740), and albumin (223).

References

Type 2 diabetes

1. CDC and Prevention. National Diabetes Statistics Report, 2022. U.S. Dept of Health and Human Services; 2022. cdc.gov/diabetes/data/statistics-report/index.html
2. Abbasi F, Shiffman D, Tong CH, et al. Insulin resistance probability scores for apparently healthy individuals. *J Endocr Soc.* 2018;2:1050-1057. doi:10.1210/js.2018-00107
3. American Diabetes Association. Standards of Care in Diabetes-2023 Abridged for Primary Care Providers. *Clin Diabetes.* 2022;41(1):4-31. doi:10.2337/cd23-as01
4. Zhu K, Wactawski-Wende J, Mendola P, et al. Adverse pregnancy outcomes and risk of type 2 diabetes in postmenopausal women. *Am J Obstet Gynecol.* 2023;S0002-9378(23)00502-1. doi:10.1016/j.ajog.2023.07.030
5. Tucker J, Salas J, Secrest S, Scherrer JF. Erectile dysfunction associated with undiagnosed prediabetes and type 2 diabetes in young adult males: A retrospective cohort study. *Prev Med.* 2023;174:107646. doi:10.1016/j.ypmed.2023.107646
6. Yao QM, Wang B, An XF, Zhang JA, Ding L. Testosterone level and risk of type 2 diabetes in men: a systematic review and meta-analysis. *Endocr Connect.* 2018;7(1):220-231. doi:10.1530/EC-17-0253
7. Rong F, Dai H, Wu Y, et al. Association between thyroid dysfunction and type 2 diabetes: a meta-analysis of prospective observational studies. *BMC Med.* 2021;19(1):257. doi:10.1186/s12916-021-02121-2
8. Monticone S, D'Ascenzo F, Moretti C, et al. Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol.* 2018;6(1):41-50. doi:10.1016/S2213-8587(17)30319-4
9. KDIGO. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl.* 2013;3(1). kdigo.org/wp-content/uploads/2017/02/KDIGO_2012_CKD_GL.pdf
10. Cusi K, Isaacs S, Barb D, et al. American Association of Clinical Endocrinology Clinical Practice Guideline for the Diagnosis and Management of Nonalcoholic Fatty Liver Disease in Primary Care and Endocrinology Clinical Settings: Co-Sponsored by the American Association for the Study of Liver Diseases (AASLD). *Endocr Pract.* 2022;28(5):528-562. doi:10.1016/j.eprac.2022.03.010

Nonalcoholic fatty liver disease

11. Rinella ME, Neuschwander-Tetri BA, Siddiqui MS, et al. AASLD Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease. *Hepatology.* 2023;77(5):1797-1835. doi:10.1097/HEP.0000000000000323
12. Bril F, McPhaul MJ, Kalavalapalli S, et al. Intact fasting insulin identifies nonalcoholic fatty liver disease in patients without diabetes. *J Clin Endocrinol Metab.* 2021;106(11):e4360-e4371. doi:10.1210/clinem/dgab417
13. Sarkar M, Yates K, Suzuki A, et al. Low testosterone is associated with nonalcoholic steatohepatitis and fibrosis severity in men. *Clin Gastroenterol Hepatol.* 2021;19(2):400-402.e2. doi:10.1016/j.cgh.2019.11.053
14. Kizivat T, Maric I, Mudri D, Curcic IB, Primorac D, Smolic M. Hypothyroidism and nonalcoholic fatty liver disease: pathophysiological associations and therapeutic implications. *J Clin Transl Hepatol.* 2020;8(3):347-353. doi:10.14218/JCTH.2020.00027

Chronic kidney disease

15. CDC and Prevention. Chronic kidney disease in the United States, 2023. cdc.gov/kidneydisease/publications-resources/ckd-national-facts.html
16. United States Renal Data System. 2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2020. usrds-adr.niddk.nih.gov/2020
17. Molnar AO, Hiremath S, Brown PA, Akbari A. Risk factors for unplanned and crash dialysis starts: a protocol for a systematic review and meta-analysis. *Syst Rev.* 2016;5(1):117. doi:10.1186/s13643-016-0297-2
18. National Kidney Foundation. Which drugs are harmful to your kidneys? 2017. kidney.org/atoz/content/drugs-your-kidneys
19. Monticone S, Sconfienza E, D'Ascenzo F, et al. Renal damage in primary aldosteronism: a systematic review and meta-analysis. *J Hypertens.* 2020;38(1):3-12. doi:10.1097/HJH.0000000000002216
20. Amiri M, Ramezani Tehrani F, Rahmati M, et al. Low serum testosterone levels and the incidence of chronic kidney disease among male adults: a prospective population-based study. *Andrology.* 2020;8(3):575-582. doi:10.1111/andr.12728
21. Narasaki Y, Sohn P, Rhee CM. The interplay between thyroid dysfunction and kidney disease. *Semin Nephrol.* 2021;41(2):133-143. doi:10.1016/j.semnephrol.2021.03.008
22. Carvalho KD, Daltro C, Rocha R, Cotrim HP. Nonalcoholic fatty liver disease: a risk factor for chronic kidney disease. *Ann Hepatol.* 2023;28(5):101122. doi:10.1016/j.aohep.2023.101122

Cardiovascular disease

23. Michos ED, Khan SS. Further understanding of ideal cardiovascular health score metrics and cardiovascular disease. *Expert Rev Cardiovasc Ther.* 2021 Jul;19(7):607-617. doi:10.1080/14779072.2021.1937127
24. McClelland RL, Chung H, Detrano R, et al. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation.* 2006;113(1):30-37. doi:10.1161/CIRCULATIONAHA.105.580696
25. Virani SS, Alonso A, Aparicio HJ, et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2021 update: a report From the American Heart Association. *Circulation.* 2021;143(8):e254-e743. doi:10.1161/CIR.0000000000000950
26. Hajar R. Risk factors for coronary artery disease: historical perspectives. *Heart Views.* 2017;18(3):109-114. doi:10.4103/HEARTVIEWS.HEARTVIEWS_106_17
27. Tsao CW, Aday AW, Almarzooq ZI, et al. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation.* 2022;145(8):e153-e639. doi:10.1161/CIR.0000000000001052
28. Visseren FLJ, Mach F, Smulders YM, et al. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J.* 2021;42(34):3227-3337. doi:10.1093/eurheartj/ehab484
29. Liccardo D, Cannavo A, Spagnuolo G, et al. Periodontal disease: a risk factor for diabetes and cardiovascular disease. *Int J Mol Sci.* 2019;20(6):1414. doi:10.3390/ijms20061414
30. Tietjens JR, Claman D, Kezirian EJ, et al. Obstructive sleep apnea in cardiovascular disease: a review of the literature and proposed multidisciplinary clinical management strategy. *J Am Heart Assoc.* 2019;8(1):e010440. doi:10.1161/JAHA.118.010440
31. Zhang J, Xu JH, Qu QQ, Zhong GQ. Risk of cardiovascular and cerebrovascular events in polycystic ovarian syndrome women: a meta-analysis of cohort studies. *Front Cardiovasc Med.* 2020;7:552421. doi:10.3389/fcvm.2020.552421
32. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. *J Urol.* 2018;200(2):423-432. doi:10.1016/j.juro.2018.03.115
33. El Khoudary SR, Aggarwal B, Beckie TM, et al. Menopause transition and cardiovascular disease risk: implications for timing of early prevention: a scientific statement from the American Heart Association. *Circulation.* 2020;142(25):e506-e532. doi:10.1161/CIR.0000000000000912

Common endocrine disorders

34. Cappola AR, Desai AS, Medici M, et al. Thyroid and cardiovascular disease. *Circulation.* 2019;139(25):2892-2909. doi.org/10.1161/circulationaha.118.036859
35. Kalra S, Aggarwal S, Khandelwal D. Thyroid dysfunction and type 2 diabetes mellitus: screening strategies and implications for management. *Diabetes Ther.* 2019;10(6):2035-2044. doi:10.1007/s13300-019-00700-4
36. Mantovani A, Nascimbeni F, Lonardo A, et al. Association between primary hypothyroidism and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Thyroid.* 2018;28(10):1270-1284. doi:10.1089/thy.2018.0257
37. Iglesias P, Bajo MA, Selgas R, Díez JJ. Thyroid dysfunction and kidney disease: an update. *Rev Endocr Metab Disord.* 2017;18(1):131-144. doi:10.1007/s11154-016-9395-7
38. Hundemer GL, Curhan GC, Yozamp N, Wang M, Vaidya A. Renal outcomes in medically and surgically treated primary aldosteronism. *Hypertension.* 2018;72(3):658-666. doi:10.1161/HYPERTENSIONAHA.118.11568
39. Oliver-Williams C, Vassard D, Pinborg A, Schmidt L. Risk of cardiovascular disease for women with polycystic ovary syndrome: results from a national Danish registry cohort study. *Eur J Prev Cardiol.* 2021;28(12):e39-e41. doi:10.1177/2047487320939674
40. Behboudi-Gandevani S, Ramezani Tehrani F, Hosseinpanah F, et al. Cardiometabolic risks in polycystic ovary syndrome: long-term population-based follow-up study. *Fertil Steril.* 2018;110(7):1377-1386. doi:10.1016/j.fertnstert.2018.08.046
41. Centers for Disease Control and Prevention. PCOS (Polycystic Ovary Syndrome) and Diabetes. 2019. cdc.gov/diabetes/basics/pcos.html
42. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care.* 2007;30(2):234-238. doi:10.2337/dc06-1579
43. Gryzinski GM, Bernie HL. Testosterone deficiency and the aging male. *Int J Impot Res.* 2022;34(7):630-634. doi:10.1038/s41443-022-00555-7
44. Romejko K, Rymarz A, Sadownik H, Niemczyk S. Testosterone deficiency as one of the major endocrine disorders in chronic kidney disease. *Nutrients.* 2022;14(16):3438. doi:10.3390/nu14163438
45. Mahalingaiah S, Sun F, Cheng JJ, Chow ET, Lunetta KL, Murabito JM. Cardiovascular risk factors among women with self-reported infertility. *Fertil Res Pract.* 2017;3(1):7. doi:10.1186/s40738-017-0034-0
46. Gleason JL, Shenassa ED, Thoma ME. Self-reported infertility, metabolic dysfunction, and cardiovascular events: a cross-sectional analysis among U.S. women. *Fertil Steril.* 2019;111:138–146. doi:10.1016/j.fertnstert.2018.10.009
47. Eisenberg ML, Li S, Cullen MR, Baker LC. Increased risk of incident chronic medical conditions in infertile men: analysis of United States claims data. *Fertil Steril.* 2016;105(3):629-636. doi:10.1016/j.fertnstert.2015.11.011

Improve patient outcomes through early identification and accurate diagnosis of the related cardiometabolic conditions.

For more information, contact your cardiometabolic account executive.

Quest Diagnostics®

QuestDiagnostics.com